Fever of Unknown Origin in a Bulgarian Hospital: Evaluation of 54 Cases for a Four Year-Period

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Abstract

Aim: The aim of this study was to describe the etiological distribution, clinical and laboratory characteristics of patients with Fever of unknown origin (FUO), admitted to one Bulgarian hospital. Material and Method: A retrospective study was done for a period of four years. The modified criteria of Petersdorf and Beeson were applied. Complete history, physical examination and basic laboratory investigations were done. According to the potentially diagnostic clues, specific tests, immunological and imaging methods were performed. The invasive procedures were the last step. Results: Fifty-four patients met the inclusion criteria. The estimated causes were: infection 59.3%, neoplasm 3.7%, non-infectious inflammatory disease 14.8%, miscellaneous 5.5% and undiagnosed cases 16.7%, respectively. The mean age was 44.3 years. The leading clinical features were fever, chills, sweats and fatigue. The association of clinical signs, physical exam and laboratory results were discussed. Discussion: The infectious diseases were the leading cause of FUO. The etiological distribution of causes was near to results reported from South-East Europe. Some geographic, climatic, zoonotic and social factors influenced the results.

Keywords

Causes; Fever; South-East Europe

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Introduction

Fever of unknown origin (FUO) is a perplexing medical problem from ancient times. The condition was defined by Petersdorf and Beeson in 1961 as an illness with following criteria [1]: (a) fever more than 38.30C at least three occasions; (b) the duration of illness at least three weeks; (c) the diagnosis uncertain after one week of hospital investigation. Due to the medical and technological progress the third criteria has been modified to three outpatient visits or three days of intensive hospital investigations [2]. Since then to our days many studies and research have been conducted. The causes of FUO are more than two hundreds diseases, which are grouped at four categories: infection, neoplasm, non-infectious inflammatory diseases (NIID), miscellaneous [1-5]. The disturbance of etiological reasons is affected by geographic and climate characteristics, economical and social factors. In Western Europe infectious diseases (ID) and NIID are almost equal, fallowing by neoplasm and undiagnosed cases [6-8]. In contrast, from a few reports from South-East Europe the ID are the most frequent causes of FUO and the undiagnosed cases are not so many [9-11].

The aim of this study was to describe the etiological distribution, clinical and laboratory characteristics of patients with FUO, admitted to one Bulgarian hospital. We performed the first retrospective study among Bulgarian patients suffering from FUO.

Material and Method

The retrospective study was conducted at the Department of Infectious Diseases, Military Medical Academy, Sofia (Bulgaria) for the period from May 2006 through May 2010. The inclusion criteria for the study were (1) patients older than 18 years-old, (2) hospitalized at the Department of Infectious Diseases, Military Medical Academy (Sofia, BG), (3) patients fulfilled the modified definition of FUO: (a) fever more than 38.30C at least three occasions, (b) the duration of illness at least three weeks, (c) the diagnosis uncertain after three outpatient visits or after three days of intensive hospital investigations [2]. The exclusion criteria are: (1) patients with HIV/AIDS, (2) known immunosuppression or malignancy, (3) people who received immunomodulatory drugs.

During the diagnostic work-up a search for potentially diagnostic clues (PDCs) was done. PDCs are defined as symptoms, localizing signs and abnormalities which point toward a diagnosis. PDCs are estimated among medical history, physical examination and laboratory data. Based on PDCs the list of probable diseases is limited. The information from PDCs is used to recommend the next diagnostic investigations.

After the detailed screening among medical records, the patients who fulfilled the inclusion criteria continued to be studied. The thorough medical history and comprehensive physical exam were drawn. Laboratory investigations included: complete blood count with differential, erythrocyte sedimentation rate (ESR), urinalysis, hemostasis, creatinine, urea, total protein, albumin-serum, aspartate transaminase (AST), alanine transaminase (ALT), creatine phosphokinase, C-reactive protein (CRP), lactate dehydrogenase (LDH), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), electrolytes.

Blood culture, urine culture and any other culture methods (samples of throat, sputum, fecal, eyes, nose, ears and etc.) depending of the clinical presentations were done.

Serological tests for infectious agents were applied basing on the clinical, epidemiological and laboratory clues. Enzyme-linked immunosorbent assay (ELISA) for IgM, IgG and IgA (where is applicable) were conducted for HAV, HCV, HBV, HEV, HIV, EBV, CMV, C.pneumoniae, M.pneumoniae, Adenovirus, C.jejuni, Y.enterocolitica, B.burgdorferi, R.conorii, L.pneumophila, C.burnetii, T.gondii, T.spiralis. Urine test for L.pneumophila also was done. Immunoblotting techniques were applied for HIV, HCV, B.burgdorferi. For T.pallidum were used the following tests Venereal Disease Research Laboratory (VDRL), Rapid Plasma Regain (RPR), Treponemal enzyme immunoassay (EIA) for IgG and IgM.

For the interpretation of the specific serological results were accepted the following formulation. The result was “true positive” when it was considered to be related to the final diagnosis. The abnormal result was categorized as “false positive” when it was not related to the illness of the final diagnosis.

Rheumatoid factor (RF), antistreptolysin titer, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, thyroid stimulating hormone, purified protein derivative (PPD), QuantiFERON-TB Gold test were the second line of investigations. The imaging studies as X-ray and abdominal ultrasound are mandatory, but echocardiography, computer tomography (CT), magnetic resonance imaging (MRI), scintigraphies depend from the presenting of potential diagnostic clues. The invasive methods were the last step of the evaluation, depending of the clinical condition and laboratory findings.

Table 1. Clinical signs and physical findings in 54 patients with FUO

Variable	Patients (n)	Contributory (%)	Non-contributory (%)
Clinical signs			
• Abdominal pain	12	50	50
• Anorexia	5	40	60
• Arthralgia	17	71	29
• Chills	30	80	20
• Cough	14	50	50
• Diarrhea	6	33	67
• Fatigue	37	84	16
• Fever	54	100	-
• Headache	9	56	44
• Muscle pain	17	53	47
• Skin rash	5	60	40
• Sweats	20	80	20
• Throat pain	6	17	83
• Weight loss	4	50	50
Physical findings			
• Adenopathy (localized)	7	29	71
• Hepatomegaly	22	73	27
• Skin rash	5	40	60
• Sore throat	23	26	74
• Splenomegaly	8	75	25

Note: ID - Infectious diseases; MD - Malignant diseases; NIID - Non-infectious inflammatory diseases; Mis - Miscellaneous; Un - Undiagnosed;

Statistical analysis was performed by Excel 2007 and SPSS Statistics 19.0 (Chicago, IL, USA). A P-value of < 0.05 was considered significant. Fisher test was used for comparing different groups.

Clinical features, physical points and diagnostic tools were analyzed as "contributory" and "non-contributory" to the final diagnosis. Any clinical signs and physical abnormality was called "contributory" or "helpful" to the diagnosis when the detected parameter was considered to be related to the final diagnosis. Respectively, we used "non-contributory" to the final diagnosis when the clinical symptoms and physical findings are not related to the final diagnosis.

The diagnostic methods are classified as "contributory" or "helpful" when the abnormal result is considered to be related to the final diagnosis, using the methods helps to the process for establishing the final diagnosis. The application of the methods is called "non-contributory" or "non-helpful" when the result of the assay is not related to the final diagnosis and doesn't help to the process of determine the final diagnosis. In conclusion we used the term "useful" for this method, which application and result are related to the final diagnosis and help to the diagnostic process. The term "usefulness" for that applying, which method is considered for "useful". The final diagnosis is based on the integrate information from medical history, clinical features, physical findings, laboratory data and diagnostics methods.

Results

Fifty-four patients met the inclusion criteria. The mean age was 44.3 years (range: 18-75). Men were 35 (64.8%). The mean hospital duration was 13 days. The mean duration of febrile syndrome up to the hospital admission was 54.6 days. The leading clinical signs were fever (100.0%), fatigue (68.5%), chills (55.6%), sweats (37.0%), muscle pain (31.5%) and arthralgia (31.5%). Symptoms as weight loss, anorexia, skin rash, throat pain, diarrhea and vomiting were too rare. The helpfulness of the clinical signs is shown at Table 1. Arthropod bites were noticed by five patients and was contributory in 80.0%. Epidemiological data for animal contact were mentioned by two men and this information was related to the final diagnosis. Physical examination found as common presentations sore throat (42.6%) and hepatomegaly (40.7%); in contrast splenomegaly and localized adenopathy were reported in 14.8% and 13%, respectively. The contributory meaning of physical findings is noted in Table 1.

The values of laboratory parameters are presented in the Table 2. An alteration of inflammatory markers as ESR and CRP were the most common establishment among patients with FUO. The increasing values of liver enzymes were observed in NIID group, dominantly.

The various culture methods were performed but the results were not statistically significant to the final diagnosis (Table 3). The serological methods were routinely used. The false positive results were estimated in 19.0% of all patients.

Table 2. Laboratory data in patients with FUO

Variable		All patients (n=54)	ID (n=32)	MD (n=2)	NIID (n=8)	Mis (n=3)	Un (n=9)	P-value
Hemoglobin (130-180 g/L)* (120-160 g/L)†	mean ± SD	126.1±18.9	129.1±18.7	N/A	126.7±15.2	N/A	113.5±23.4	
	LLN (%)	37.0	31.2	N/A	37.5	N/A	66.7	0.182
White blood cells (3.5-10.5 x109/L)	mean ± SD	8.2±2.7	7.9±2.7	N/A	8.8±3.3	N/A	8.1±2.2	
	ULN (%)	16.6	18.7	N/A	25.0	N/A	11.1	0.755
Erythrocyte sedimentation rate (≤ 20 mm/h)	mean ± SD	59.5±38.9	47.8±34.1	N/A	61.3±40.8	N/A	91.7±41.0	
	ULN (%)	81.5	75.0	N/A	75.0	N/A	100.0	0.293
Fibrinogen (2.0-4.5 g/L)	mean ± SD	6.8±2.3	6.2±2.3	N/A	6.8±3.0	N/A	8.2±1.7	
	ULN (%)	61.1	53.1	N/A	75.0	N/A	77.7	0.355
C-reactive protein (0.0-5.0 mg/L)	mean ± SD	60.8±64.6	39.3±47.4	N/A	73.7±60.5	N/A	118.9±93.8	
	ULN (%)	87.8	78.3	N/A	100.0	N/A	100.0	0.175
Aspartate transaminase (5-40 IU/L)	mean ± SD	34.3±32.6	32.8±29.2	N/A	41.8±49.3	N/A	26.0±6.7	
	ULN (%)	13.2	12.5	N/A	12.5	N/A	11.1	1.000
Alanine transaminase (5-40 IU/L)	mean ± SD	49.4±43.7	43.8±36.1	N/A	73.1±68.7	N/A	38.3±20.6	
	ULN (%)	43.4	37.5	N/A	62.5	N/A	44.4	0.448
Gamma-glutamyl transferase (10-50 IU/L)	mean ± SD	118.6±145.1	84.7±94.5	N/A	116.5±145.7	N/A	136.0±66.3	
	ULN (%)	56.0	43.3	N/A	62.5	N/A	87.5	0.078
Alkaline phosphatase (64-300 IU/L)	mean ± SD	285.2±171.8	244.6±132.9	N/A	236.1±73.9	N/A	451.8±244.8	
	ULN (%)	22.2	18.7	N/A	12.5	N/A	44.4	0.280
Creatine phosphokinase (< 190 IU/L)	mean ± SD	85.8±109.8	109.0±134.6	N/A	40.2±29.3	N/A	43.4±18.5	
	ULN (%)	14.7	20.0	N/A	0.0	N/A	0.0	0.420
Lactate dehydrogenase (208-378 IU/L)	mean ± SD	620.9±589.6	678.0±760.5	N/A	793.0±584.0	N/A	425.0±32.5	
	ULN (%)	63.6	50.0	N/A	100.0	N/A	100.0	N/A

Note: ID - Infectious diseases; MD - Malignant diseases; NIID - Non-infectious inflammatory diseases; Mis - Miscellaneous; Un - Undiagnosed; SD - Standard deviation; LLN – lower limit of normal; ULN - upper limit of normal; N/A - not applicable; * - male; † - female;

Based on the history, physical check in, laboratory investigations, cultures, serological tests and imaging methods the final diagnosis was estimated in forty-five of cases with FUO. The distribution by causes among diagnosed cases is follow: infection 71.1%, neoplasm 4.4%, non-infectious inflammatory disease 17.8%, miscellaneous 6.7%. The undiagnosed cases are nine. The etiological causes are presented in Table 4. The patients with established infectious etiological agents were treated at the Department of Infectious Diseases, Military Medical Academy (Sofia, BG). Other diagnosed cases were transferred to the special department according by the estimate diagnosis.

Discussion

We present the first report of FUO from Bulgaria in the English language literature (Medline, 1961-2015). The retrospective study estimated infections as the leading causes of FUO. Neighboring countries as Serbia and Turkey reported similar high percentage for infectious diseases (Table 5). The region of South-East Europe is characterized by special endemic infections and features of medical support. The reports from West Europe estimated that NIID and ID are the main causes, and NIID is the leader (Table 5). These results correspond to the geographic and economical characteristics of the countries, the absence of endemic diseases and the high development of medical techniques.

One more explanation of the high percentage of ID in Bulgaria is the restriction of this study, which is performed at the Department of Infectious Diseases; patients are guided to the department with suspicion of ID. The design of the study is other reason: (1) it is retrospective, conducted in one hospital; (2) it is not a multicentre project. Nevertheless, except of these limitations, ID should be again the leader because of the local geo-

Table 3. The contributory meanings of the diagnostic methods to the final diagnosis

Diagnostic Method (%)	All patients (%)	ID (%)	MD (%)	NIID (%)	Mis (%)	Un (%)	Helpful in all patients (%)
Blood culture	63	56	ND	88	100	67	3
Urine culture	59	56	50	50	100	67	6
Throat culture	59	63	50	50	67	56	3
Fecal culture	32	38	50	25	ND	22	18
Sputum culture	9	6	ND	25	33	ND	0
Infectious serology	98	97	100	100	100	100	47
Thyroid hormones	22	19	ND	38	100	ND	25
X-ray	54	53	100	63	ND	56	21
Abdominal US	61	59	100	50	67	67	45
Echocardiography	35	34	ND	38	ND	56	21
Computed tomography	20	19	ND	38	33	11	64

Note: ID - Infectious diseases; MD - Malignant diseases; NIID - Non-infectious inflammatory diseases; Mis - Miscellaneous; Un - Undiagnosed; US - ultrasonography; ND - no data available;

Table 4. The final diagnosis in patients with fever of unknown origin

Infectious diseases (32)	Malignant diseases (2)	Non-infectious inflammatory diseases (8)	Miscellaneous (3)
Q-fever (5) Legionellosis (3) Lyme Disease (2) Trichinellosis (2) Mediterranean Spotted Fever (2) M. Pneumoniae (2) M. Pneumoniae + Adenovirus (1) M. Pneumoniae + Epstein–Barr Virus (1) C. Pneumoniae (1) C. Pneumoniae + Adenovirus (1) C. Pneumoniae + Q-fever (1) Legionellosis + HCV-infection (1) Pericarditis (1) Eye Infection (1) Typhus Abdominis (1) Salmonellosis (1) Campylobacteriosis (1) Yersiniosis (1) Shigellosis (1) Cholecystitis (1) Abdominal Abscess (1) Urinary Tract Infection (1)	Breast Carcinoma (1) Myeloproliferative Disorders (1)	Adult-Onset-Still-Disease (5) Polymyalgia Rheumatica (2) Myositis (1)	Thyroiditis (3)
Undiagnosed (9)			

Table 5. Comparison of the diagnostic categories in FUO reported from USA, Western Europe and South-East Europe

Variable	References study												Present Study
	[1]	[12]	[13]	[14]	[15]	[16]	[17]	[18]	[9]	[19]	[20]	[21]	
Publication date	1961	1982	1992	1997	2003	2009	2003	2005	2008	2010	2011	2012	2016
Country	USA	USA	USA	Netherlands	Belgium	France	Romania	Turkey	Turkey	Greece	Serbia	Turkey	Bulgaria
Patients, n	100	105	86	123	290	280	164	59	154	112	100	100	54
Diagnosis, %	91.0	83.8	90.7	68.3	66.2	67.1	92.7	88.1	84.4	79.5	78.0	80.0	83.3
No diagnosis, %	9.0	16.2	9.3	31.7	33.8	32.9	7.3	11.9	15.6	20.5	22.0	20.0	16.7
Diagnostic categories, % of diagnosed cases													
• ID	39.6	36.4	35.9	33.3	29.7	16.0	48.7	59.6	40.8	38.2	69.2	32.5	71.1
• MD	20.9	37.5	26.9	16.7	15.1	30.3	27.0	19.2	16.9	13.5	15.4	17.5	4.4
• NIID	18.7	14.8	23.1	38.1	35.4	40.4	19.7	21.2	36.2	41.6	15.4	47.5	17.8
• Mis	20.8	11.3	14.1	11.9	19.8	13.3	4.6	-	6.1	6.7	-	2.5	6.7

Note: ID - Infectious diseases; MD - Malignant diseases; NIID - Non-infectious inflammatory diseases; Mis - Miscellaneous;

graphic, endemic and social factors as a prevalence of endemic diseases, poor health care controls, the lack of collaboration by institutions, existence of developing population without medical education and access to adequate medical support.

The study defined fever, chills, sweats and fatigue as main symptoms in case of FUO. They were used as PDCs for the diagnostic process. From the physical examination only hepatomegaly was considered to be helpful to the final diagnosis and was mention for PDC. The results of laboratory parameters are not statistically associated with actual etiologic group of causes (P-value > 0.05, Table 2). So, we cannot use any abnormal result as a marker for each specific etiological group of FUO. In general the elevation of acute phase reactants is basic abnormality in case of FUO with high prevalence in group of ID and NIID. The increasing of liver enzymes is more common in NIID and undiagnosed group compared with ID. The using of culture methods in the study was non-contributory to the final diagnosis. The reason is the frequent prescription of antibiotics of general practitioners early in the febrile illness without appliance of appropriate culture diagnostic methods. The serological methods are helpful but the opportunity for false positive results has to be kept in mind. These false positive results let to delaying of final diagnosis in group of neoplasm, NIID and miscellaneous. The performance of the imaging methods showed the highest usefulness of CT, following by abdominal ultrasound and X-ray for the diagnostic process (Table 3). The helpfulness of X-ray was not high but the probability of disorder exists and this imaging method should be a step in the diagnostic protocol. This recommendation is done by other authors [9, 22]. The present study confirmed the helpfulness of the ultrasound and CT in the diagnostic protocol for FUO. The literature review shows that invasive methods are significant step in the diagnostic algorithm [9, 21, 23], but in the present study they are performed in a few patients and the results are not applicable. For future national study we recommend broad application of imaging methods, nuclear technics and invasive procedures as a step of the diagnostic protocol [24].

In conclusion, it can be summarized that patients with FUO are rare, but are diagnostic challenge. It is needed a complex and general medical collaboration to find the real final diagnosis. The distribution by causes is influenced by some factors such as geographic location, zoonotic characteristics and landscape, economical development of the country and medical organization of health care system. Based on these components we can explain the leader place of ID as a cause of FUO in Bulgaria. Cases of FUO were described with various clinical signs and abnormalities of physical exam should be search more active. Most of the cases were presented with increasing of acute phase proteins; anemia is associated with neoplasm, the alteration of liver and biliary function is usually presents in cases of NIID and undiagnosed patients.

The study shows the main role of the infectious illness as a cause of perplexing prolonged fever in Bulgaria. Consequently any case of FUO in our country should be first observed by ID specialist. After rejecting the infectious disease as a cause, the patient should be directed to department of internal medicine for future investigations.

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Conflicts of interest

None of the authors have any associations that might be deemed a conflict of interest to the publication of this manuscript.

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Competing interests

The authors declare that they have no competing interests.

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